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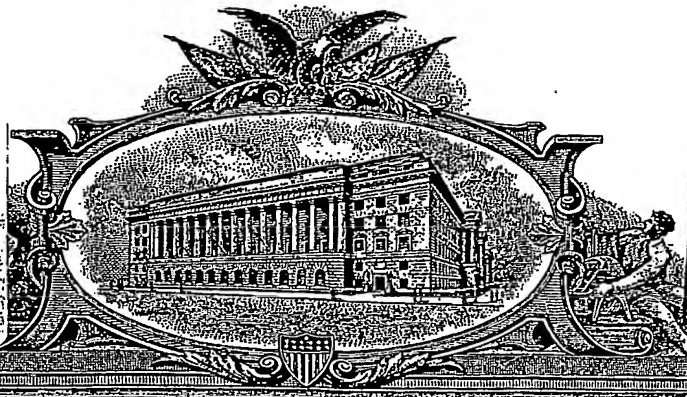

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P-16180

SULFONAMIDE DERIVATIVES AS PPAR MODULATORS

FIELD OF THE INVENTION

The present invention relates to compounds of peroxisome proliferator activated receptor (PPAR) agonists, more specifically sulfonamide derivatives of PPAR agonists, which are useful for the treatment and/or prevention of disorders modulated by a PPAR agonist.

BACKGROUND OF THE INVENTION

The peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor gene family that are activated by fatty acids and fatty acid metabolites. The PPARs belong to the subset of nuclear receptors that function as heterodimers with the 9-*cis* retinoic acid receptor (RXR). Three subtypes, designated PPARα, PPARγand PPARδ, are found in species ranging from *Xenopus* to humans.

PPARα is the main subtype in the liver and has facilitated analysis of the mechanism by which peroxisome proliferators exert their pleiotropic effects. PPARα is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β-oxidation of fatty acids. PPARα is also involved with the activity of fibrates and fatty acids in rodents and humans. Fibric acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma triglycerides along with moderate reduction in low-density lipoprotein (LDL) cholesterol, and they are used particularly for the treatment of hypertriglyceridemia.

PPARγ is the main subtype in adipose tissue and involved in activating the program of adipocyte differentiation. PPARγ is not involved in stimulating peroxisome proliferation in the liver. There are two isomers of PPARγ: PPARγ1 and PPARγ2, which differ only in that PPARγ2 contains an additional 28 amino acids present at the amino terminus. The DNA sequences for the PPARγ receptors are described in Elbrecht, et al., BBRC 224;431-437 (1996). Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J_2 derivatives have been identified as natural ligands for PPARγ, which also binds the anti-diabetic agents thiazolidinediones with high affinity. The physiological functions of PPARα and PPARγ in lipid and carbohydrate metabolism were uncovered once it was recognized that they were the receptors for the fibrate and glitazone drugs, respectively.

PPARα and PPARγ receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, and gastrointestinal disease, such as inflammatory bowel disease and other inflammation related illnesses. Such inflammation related illnesses include, but are not limited to Alzheimer's disease, Crohn's disease, rheumatoid arthritis, psoriasis, and ischemia reprofusion injury.

By contrast, PPARδ (also referred to as PPARβ and NUC1) is not reported to be receptor for any known class of drug molecules, and its role in mammalian physiology has remained undefined. The human nuclear receptor gene PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, 6:1634-1641 (1992).

Diabetes is a disease in which a mammal's ability to regulate glucose levels in the blood is impaired because the mammal has a reduced ability to convert glucose to glycogen for storage in muscle and liver cells. In Type I diabetes, this reduced ability to store glucose is caused by reduced insulin production. "Type II Diabetes" or "non-insulin dependent diabetes mellitus" (NIDDM) is the form of diabetes, which is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. When these cells become

desensitized to insulin, the body tries to compensate by producing abnormally high levels of insulin and hyperinsulemia results. Hyperinsulemia is associated with hypertension and elevated body weight. Since insulin is involved in promoting the cellular uptake of glucose, amino acids and triglycerides from the blood by insulin sensitive cells, insulin insensitivity can result in elevated levels of triglycerides and LDL (known as the "bad" cholesterol) which are risk factors in cardiovascular diseases. The constellation of symptoms which includes hyperinsulemia combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL is known as Syndrome X.

Hyperlipidemia is a condition which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The initial treatment for hypercholesterolemia is often a diet low in fat and cholesterol coupled with appropriate physical exercise. Drug intervention is initiated if LDL-lowering goals are not met by diet and exercise alone. It is desirable to lower elevated levels of LDL cholesterol and increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373- 381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL elevation are associated with undesirable effects, such as flushing.

There are several treatments currently available for treating diabetes mellitus but these treatments still remain unsatisfactory and have limitations. While physical exercise and reduction in dietary intake of calories will improve the diabetic condition, compliance with this approach can be poor because of sedentary lifestyles and excess food consumption, in particular high fat-containing food. Therefore, treatment with hypoglycemics, such as sulfonylureas (e.g., chlorpropamide, tolbutamide, tolazamide and acetohexamide) and biguanides (e.g. phenformin and metformin) are often necessary as the disease progresses. Sulfonylureas stimulate the β cells of the pancreas to secrete more insulin as the disease progresses. However, the response of the β cells eventually fails and treatment with insulin injections is necessary. In addition,

both sulfonylurea treatment and insulin injection have the life threatening side effect of hypoglycemic coma, and thus patients using these treatments must carefully control dosage.

It has been well established that improved glycemic control in patients with diabetes (Type I and Type II) is accompanied by decreased microvasclular complications (DCCT and UKPDS). Due to difficulty in maintaining adequate glycemic control over time in patients with Type II diabetes, the use of insulin sensitizers in the therapy of Type II diabetes is growing. There is also a growing body of evidence that PPARγ agonist, insulin sensitizer, may have benefits in the treatment of Type II diabetes beyond their effects in improving glycemic control.

In the last decade a class of compounds known as thiazolidinediones (e.g. U.S. Pat. Nos. 5,089,514; 4,342,771; 4,367,234; 4,340,605; and 5,306,726) have emerged as effective antidiabetic agents that have been shown to increase the sensitivity of insulin sensitive tissues, such as skeletal muscle, liver and adipose, to insulin. Increasing insulin sensitivity rather than the amount of insulin in the blood reduces the likelihood of hypoglycemic coma. Although thiazolidinediones have been shown to increase insulin sensitivity by binding to PPARγ receptors, this treatment also produces unwanted side effects such as weight gain and, for troglitazone, liver toxicity.

In view of the above, there exists a need for new pharmaceutical agents which modulate these receptors to prevent, treat and/or alleviate these diseases or conditions while ameliorating side effects of current treatments.